
A novel bone morphogenetic protein signaling in heterotypic cell interactions in prostate cancer.

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Public Summary:

Scientific Abstract:

We examined the effect of the extracellular bone morphogenetic protein (BMP) 2 and 7, which are up-regulated in the prostate adenocarcinomas of the conditional Pten deletion mouse model, on primary cultures of cancer-associated fibroblasts (CAF) derived from these tumors. In the CAF, we show that BMP2 or BMP7, but not transforming growth factor beta-1, can strikingly stimulate secretion of stromal cell-derived factor-1 (SDF-1), also known as CXCL12. The CAF cells express type I and type II BMP receptors as well as the receptor for SDF-1, CXCR4. SDF-1 activation is associated with BMP-induced Smad phosphorylation, and the stimulatory effect is blocked by BMP antagonist, noggin. The findings that BMP treatment can increase SDF-1 pre-mRNA levels in a time-dependent manner and actinomycin D treatment can abolish stimulatory effect of BMP suggest a transcriptional modulation of SDF-1 by BMP signaling. Using a human microvascular endothelial cell line, we show that SDF-1 present in the conditioned medium from the stimulated CAF can significantly induce tube formation, an effect relating to angiogenic function. Furthermore, we found that BMP2 can also protect the CAF from serum starvation-induced apoptosis independent of SDF-1, implying that BMP may induce other factors to sustain the survival of these cells. In short, this report establishes a novel BMP-SDF-1 axis in the prostate tumor along with a new prosurvival effect of BMP that when considered together with our previously described oncogenic properties of BMP indicate a circuitry for heterotypic cell interactions potentially critical in prostate cancer.

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